jc598 U.S. PTO 12/11/98

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PTO/SB/05 (4/98)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	E-1537 CIP
First Inventor or Application Identifier	Anna Gutowska
Title	Reversible geling copolymer and method..
Express Mail Label No.	EE277182424US

jc518 U.S. PTO 09/209541 12/11/98

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [X] * Fee Transmittal Form *(e.g., PTO/SB/17)* *(Submit an original and a duplicate for fee processing)*
2. [X] Specification [*Total Pages* 29] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [X] Drawing(s) *(35 U.S.C. 113)* [*Total Sheets* 3]
4. Oath or Declaration [*Total Pages* 3]
   - a. [X] Newly executed (original or copy)
   - b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d)) *(for continuation/divisional with Box 16 completed)*
     - i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

** NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).*

5. [ ] Microfiche Computer Program *(Appendix)*
6. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   - a. [ ] Computer Readable Copy
   - b. [ ] Paper Copy (identical to computer copy)
   - c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [X] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
13. [X] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
15. [ ] Other: .....

16. If a **CONTINUING APPLICATION**, *check appropriate box, and supply the requisite information below and in a preliminary amendment:*

[ ] Continuation [ ] Divisional [X] Continuation-in-part (CIP) of prior application No: 08/870,368

Prior application information: Examiner _____ *Group / Art Unit:* _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

[ ] *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* or [X] *Correspondence address below*

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Name (Print/Type)	Paul W. Zimmerman	*Registration No. (Attorney/Agent)*	34,761
Signature	Paul W. Zimmerman	*Date*	98/DEC/11

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Patent fees are subject to annual revision on October 1.
These are the fees effective October 1, 1997.
Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.
See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT ($) 653.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Anna Gutowska
Examiner Name	
Group / Art Unit	
Attorney Docket No.	E-1537 CIP

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 02-1275

Deposit Account Name: Battelle Memorial Institute, Pacific Northwest Division

[X] Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17

[ ] Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance

2. [ ] Payment Enclosed: [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	380
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 380.00

2. EXTRA CLAIM FEES

	Extra Claims		Fee from below	Fee Paid
Total Claims 46	-20** = 26	X	9	= 234
Independent Claims 4	- 3** = 1	X	39	= 39
Multiple Dependent				=

**or number previously paid, if greater; For Reissues, see below

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	82	209	41	** Reissue independent claims over original patent
110	22	210	11	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 273

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,510	218	755	Extension for reply within fourth month	
128	2,060	228	1,030	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,320	241	660	Petition to revive - unintentional	
142	1,320	242	660	Utility issue fee (or reissue)	
143	450	243	225	Design issue fee	
144	670	244	335	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) -0-

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Paul W. Zimmerman			Reg. Number	34,761
Signature	Paul W. Zimmerman	Date	98/DEC/11	Deposit Account User ID	005055

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Express Mailing Label #EE277182424US
PATENT
File No. E-1537 CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant or Patentee: Anna Gutowska

Serial or Patent No.: _____

Filed or Issued: _____

For: REVERSIBLE GELING CO-POLYMER AND METHOD OF MAKING

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION Battelle Memorial Institute
Pacific Northwest Division

ADDRESS OF ORGANIZATION Post Office Box 999, Richland, WA 99352

TYPE OF ORGANIZATION:

[X] Nonprofit Scientific or Educational Under Statute of State of the United States of America
(Name of State Ohio)
(Citation of Statute Sections 1719.01 and 1719.05, Rev. Code of Ohio)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled REVERSIBLE GELING CO-POLYMER AND METHOD OF MAKING by inventor(s) Anna Gutowska described in

[ ] application executed _____

[X] specification filed herewith

[ ] application serial no. _____, filed _____

[ ] patent no. _____, issued _____.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME NONE
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Paul W. Zimmerman
TITLE OF ORGANIZATION Contracting Officer, Pacific Northwest Division, Battelle Memorial Institute
ADDRESS OF PERSON SIGNING Post Office Box 999, Richland, WA 99352

SIGNATURE Paul W. Zimmerman DATE 98/Dec/11

Express Mailing Label #EE277182424US
PATENT
File No. E-1537 CIP

REVERSIBLE GELING CO-POLYMER AND METHOD OF MAKING

This invention was made with Government support under Contract DE-AC06 76RLO 1830 awarded by the U.S. Department of Energy. The Government has certain rights in the invention.

This application is a Continuation-In-Part of application serial number 08/870,368 filed 06/06/97, now _____.

FIELD OF THE INVENTION

The present invention relates generally to a reversible gel and method of making same. More specifically, the gel is a random copolymer of an [meth-]acrylamide derivative with a hydrophilic comonomer.

As used herein, the term [meth-]acrylamide denotes methacrylamide, acrylamide, or combinations thereof.

As used herein, the chemical prefix "N-" denotes "N-" "N,N-", or combinations thereof. For example N-akyl substituted (meth-) acrylamide means N-akyl substituted (meth-) acrylamide, N,N-akyl substituted (meth-) acrylamide, or combinations thereof.

BACKGROUND OF THE INVENTION

Stimuli-sensitive reversible hydrogels are herein defined as copolymer-solvent systems that undergo a transition between a solution and a gel state in response to

the external stimuli such as temperature, pH, ionic strength, solvent composition, sheer stress or a combination of these factors. A reversible stimuli-sensitive gel is one in which the transition is reversed upon reversal of the stimulus. A well known example of a reversible hydrogel is an aqueous solution of gelatin that is in a solution state at high temperatures (e.g. 80°C) and forms a gel at lower temperatures (e.g., 20°C). Other examples of reversible gels involve aqueous solutions of agarose and kappa-carrageenan that gel in response to the temperature change, and aqueous solutions of alginate that gel in response to the increased concentration of calcium ions. Reversible hydrogel systems are used in food and pharmaceutical industries as thickeners and suspending agents.

Some specific reversible geling copolymers were also investigated as drug delivery systems and tissue engineering polymer matrices. High viscosity aqueous solutions containing 20 (or more) wt.% of block copolymers of polyethylene oxide and polypropylene oxide, e.g. Poloxamer 407 and Pluronic F68 (Poloxamer 188) exhibit reverse thermal gelation. Solutions of Poloxamer 407 have been investigated for intraocular administration. Solutions containing 25 and 30 wt % of Poloxamer 407 have been prepared and the force needed to inject them through a 25 GA needle was investigated. It was concluded that a liquid-gel transition occurred inside the needle, due to the heat transfer between the needle walls and the surroundings. [J. Juhasz, A. Cabana, A. Ait-Kadi, EVALUATION OF THE INJECTION FORCE OF POLOXAMER 407 GELS FOR INTRAOCULAR ADMINISTRATION, Pharm.Res., 13, No.9, 1996, Symposium Supplement, S-276].

In another example, 25 wt.% aqueous solution of

Pluronic F68 was mixed with articular chondrocyte cells suspension at 4°C and injected subcutaneously in nude and immunocompetent rabbit. In both cases, the cells entrapped in the copolymer formed tissue with histological appearance of hyaline cartilage. It was concluded that thermally reversible Pluronic F68 gel can serve as an effective injectable matrix for tissue engineering. [C.A.Vacanti, et al., Proceedings of Tissue Engineering Society, Orlando, FL, 1996]

An example of a pH-reversible hydrogel, investigated as an in situ geling system for ophthalmic use is the aqueous solution of, a poly(acrylic acid)polymer, which undergoes a pH-mediated phase transition at concentrations above 0.1 wt.%. The solution also contains hydroxypropyl methylcellulose, a viscosity enhancing agent. [Pharm.Res., 13, No.9, 1996, Symposium Supplement].

A new vehicle for topical and mucosal delivery, based on reversible gelation, was developed as an interpenetrating polymer network (IPN) of poly(acrylic acid) and a block copolymer of poly(ethylene oxide)/poly(propylene oxide). When heated from ambient to body temperature the network exhibited a significant viscosity increase from a viscous liquid to a gel-like consistency. It was concluded that at higher temperature, reduced release rates of active ingredients from the network were observed due to the increased viscosity of the IPN. [E.S. Ron, et al., A NEW VEHICLE FOR TOPICAL AND MUCOSAL DRUG DELIVERY, Pharm.Res., 13, No.9, 1996, Symposium Supplement, S-299].

All gels containing the copolymers of poly(ethylene oxide)/ poly(propylene oxide), i.e., Poloxamer 407, Pluronic F68 (Poloxamer 188), an IPN of poly(acrylic acid) and a

block copolymer of poly(ethylene oxide)/ poly(propylene oxide), and combinations thereof exhibit a limited, concentration dependent, stability of the gel state. The gels formed from these copolymers become liquids upon dilution (as for example due to the dilution with body fluids after peritoneal injection). Additionally, all the above examples of reversible hydrogels exhibit high initial viscosity in a liquid state, i.e., before the geling transition.

Accordingly there is a need for a reversible gel that only reverses when a specific stimulus is reversed and does not reverse upon introduction of a different stimulus (e.g. dilution). Moreover, there is a need for a reversible gel that has a lower initial viscosity.

The U.S. patent 5,262,055 to Bae et al. discusses an artificial pancreas utilizing reversible gels based on NiPAAM and its copolymers. These polymers and copolymers do not reverse upon dilution and they have a lower initial viscosity. However, the NiPAAM homopolymer described in Example 1 of Bae et al. forms a dense gel with minimal water content (i.e. exhibits substantial syneresis).

Accordingly, there remains a need for a thermally reversible gel without substantial syneresis.

Polymers exhibiting phase transitions in water have many potential uses for drug delivery as stated in GRAFT COPOLYMERS THAT EXHIBIT TEMPERATURE-INDUCED PHASE TRANSITIONS OVER A WIDE RANGE OF pH, G. Chen, AS Hoffman, Nature, Vol 373, 5 Jan 1995 (pp49-52). In this paper, the authors further describe a temperature sensitive polymer that phase separates with a change in temperature or pH. Chen and Hoffman use graft copolymers having side chains of

a temperature sensitive homopolymer, the oligo-N-isopropylacrylamide, grafted onto a pH sensitive homopolymer of acrylic acid. The authors describe the phase separation of the graft copolymer investigated by a cloud point determination in dilute solutions. However, a dilute solution cannot produce a reversible gelation of these graft copolymers. Chen and Hoffman also mention random copolymers of N-isopropylacrylamide and acrylic acid as exhibiting a phase separation, however, there is no description of the intention to study the possibility of reversible gelation in more concentrated solutions of these random copolymers.

The reversible gel of the present invention is useful as a therapeutic agent carrier, for example chemo-embolic material. Chemo-embolic materials are used in treatment of unresectable liver malignancies by a procedure called transcatheter arterial chemo-embolization. The aim of this procedure is to provide therapeutic embolization of the proper hepatic artery and localize the delivery of chemoterapeutic agents. Currently, the procedure is conducted using iodized oil and small pieces of gelatin foam. These materials are not efficient and research continues for finding new materials for chemo-embolization. Accordingly, there is a need for improved chemo-embolization material(s).

SUMMARY OF THE INVENTION

The present invention is a thermally reversible gel or thermally reversible geling copolymer that is a random copolymer of an [meth-]acrylamide derivative and a hydrophilic comonomer, wherein the random copolymer is in

the form of a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff. The thermally reversible geling copolymer is enhanced by either combining it with a therapeutic agent in an aqueous solution containing the thermally reversible geling copolymer, and/or by grafting the thermally reversible gelling copolymer to a biodegradable polymer.

The method of the present invention for making a thermally reversible geling copolymer has the steps of:

(a) mixing an [meth-]acrylamide derivative with a hydrophilic comonomer in a solvent with an initiator forming a reaction mixture;

(b) polymerizing the reaction mixture and forming a first random copolymer having a plurality of linear chains having a plurality of molecular weights; and

(c) purifying the polymerized first random copolymer and obtaining a second random copolymer having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff. The method has the further steps of combining the thermally reversible gelling copolymer with either a therapeutic agent in an aqueous solution containing the thermally reversible geling copolymer, and/or with a biodegradable polymer.

Advantages of the present invention include (1) the thermally reversible gel of the present invention exhibits a thermodynamic stability, and when geled, will not reverse to the liquid state upon dilution but may reverse to the liquid state only in response to a temperature change. Moreover, the thermally reversible gel of the present invention in a solution state has lower initial viscosity more suitable for

tissue perfusion.

It is an object of the present invention to provide a therapeutic agent carrier.

It is a further object of the present invention to provide a method of making a therapeutic agent carrier.

It is a further object of the present invention to provide a biodegradable thermally reversible graft copolymer.

The subject matter of the present invention is particularly pointed out and distinctly claimed in the concluding portion of this specification. However, both the organization and method of operation, together with further advantages and objects thereof, may best be understood by reference to the following description taken in connection with accompanying drawings wherein like reference characters refer to like elements.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a depiction of a random copolymer of poly(N-isopropylacrylamide-co-acrylic acid) (NiPAAm/AAc), where n and m denote sequences of NiPAAm and AAc (respectively) that are of random length and are randomly distributed along the copolymer chain.

FIG. 2 is a bar graph of water retention in the gel versus initial copolymer concentration in the geling solution.

FIG. 3 is a graph of fraction of 5-fluorouracil (5FU) released versus time from NiPAAm/AAc copolymer with two different drug loading percentages (20 and 33 wt% of 5FU).

FIG. 4a depicts a lymph node sectioned after the

injection of thermally reversible copolymer/dye solution.

FIG. 4b depicts another lymph node sectioned after the injection of the dye solution alone.

DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

The present invention is a thermally reversible copolymer that is useful as a gel that forms without substantial syneresis when the thermally reversible copolymer is in an aqueous solution. Syneresis is defined as water expelled from a copolymer matrix upon gelation. Substantial syneresis is more than about 10 wt% water expelled from the copolymer matrix. According to the present invention, it is preferred that the syneresis be less than about 10 wt%, more preferably less than about 5 wt% and most preferably less than about 2 wt%. Substantially no syneresis is syneresis of less than about 2 wt%, preferably 0 wt%.

The thermally reversible copolymer is a linear random copolymer of an [meth-]acrylamide derivative and a hydrophilic comonomer wherein the linear random copolymer is in the form of a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff. According to the present invention, the minimum geling molecular weight cutoff is at least several thousand and is preferably about 12,000. The presence of a substantial amount of copolymer or polymer chains having molecular weights less than the minimum geling molecular weight cutoff results in a milky solution that does not gel. Further, the amount of hydrophilic comonomer in the linear random copolymer is

preferably less than about 10 mole%, more preferably less than about 5 mole% and most preferably about 2 mole%. When the hydrophyllic comonomer is AAc and the thermosensitive co-monomer is NiPAAm, the amount of AAc in the linear random copolymer is preferably from about 1 mole % to about 2.5 mole%, most preferably from about 1.6 mole% to about 1.9 mole%. The structure of linear chains is not cross linked. Moreover, the linear random copolymer structure is one in which a linear chain **100** is shared by randomly alternating portions of the [meth-]acrylamide derivative **102** and the hydrophilic comonomer **104** as depicted in **FIG. 1.**

The [meth-]acrylamide derivative is an N-alkyl substituted [meth-]acrylamide including but not limited to N-isopropyl[meth-]acrylamide, N,N-diethyl[meth-]acrylamide, N-[meth-]acryloylpyrrolidine, N-ethyl[meth-]acrylamide, and combinations thereof.

The hydrophilic comonomer is any hydrophilic comonomer that co-polymerizes with the [meth-]acrylamide derivative. Preferred hydrophilic comonomers are hydrophilic [meth-]acryl- compounds including but not limited to carboxylic acids, [meth-]acrylamide, hydrophilic [meth-]acrylamide derivatives, hydrophilic [meth-]acrylic acid esters. The carboxylic acid may be, for example, acrylic acid, methacrylic acid and combinations thereof. The hydrophilic acrylamide derivatives include but are not limited to N,N-diethyl[meth-]acrylamide, 2-[N,N-dimethylamino]ethyl[meth-]acrylamide, 2-[N,N-diethylamino]ethyl[meth-]acrylamide, or combinations thereof. The hydrophilic [meth-]acrylic esters include but are not limited to 2-[N,N-diethylamino]ethyl[meth-]acrylate, 2-[N,N-dimethylamino]ethyl[meth-]acrylate, and combinations

thereof.

According to the present invention, the thermally reversible polymer may be mixed with an aqueous solvent to form a thermally reversible geling solution or reversible geling solution. The aqueous solvent includes but is not limited to water and aqueous salt solutions. The salt solution is preferably a phosphate buffered saline solution for medical use.

The method of making the thermally reversible polymer according to the present invention has the steps of:

(a) mixing an [meth-]acrylamide derivative with a hydrophilic comonomer in a reaction solvent with an initiator forming a reaction mixture;

(b) polymerizing the reaction mixture and forming a first linear random copolymer having a plurality of linear chains having a plurality of molecular weights; and

(c) isolating and purifying the polymerized first linear random copolymer and obtaining a second linear random copolymer having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff.

The alternatives for the [meth-]acrylamide derivative and the hydrophilic comonomer have been set forth above and are not repeated here.

The reaction solvent may be aqueous or non-aqueous. The preferred aqueous solvent is simply water. Alternatively, the aqueous solvent is a salt solution. The non-aqueous solvent may be a hydrocarbon including but not limited to oxygenated hydrocarbon solvent, for example dioxane, chlorinated hydrocarbon solvent, for example

chloroform, an aromatic hydrocarbon, for example benzene. Precipitation of the polymer occurs during polymerization in benzene. Dioxane is the preferred solvent because there is no precipitation during copolymerization thereby imparting greater uniformity of composition of the random copolymer (NiPAAM/AAc).

The amount of aqueous solvent with respect to [meth-]acrylamide derivative is preferably about 80 wt%, but may range from about 30 wt% to about 98 wt%. The amount of non-aqueous solvent with respect to the [meth-]acrylamide derivative is preferably about 80 wt% but may range from about 30 wt% to about 98 wt%.

The initiator may be any free radical initiator compatible with the [meth-]acrylamide derivative. The preferred initiator is 2,2'-azobis-isobutyrolnitrile (AIBN). The amount of the initiator with respect to the reaction mixture of solvent and polymer is preferably about 0.1 wt% but may range from about 0.01 wt% to about 2 wt%.

A reversible geling solution is made by mixing the thermally reversible polymer with an aqueous solution. The amount of aqueous solution with respect to polymer is from about 70 wt% to about 99 wt%, preferably about 98 wt% for NiPAAm/AAc to achieve a nonresorbable reversible gel with substantially no syneresis. The aqueous solution is preferably a salt solution.

In addition to the nonresorbable reversible gel composed of a linear random copolymer of N-isopropyl[meth-]acrylamide and [meth-]acrylic acid described in this invention, a biodegradable (resorbable) copolymer exhibiting similar gelation properties is obtained by grafting of the oligo [meth-]acrylamide derivative side chains on a

biodegradable polymer of, e.g., polyaminoacids, poly(phosphasenes), poly(caprolactone), polypeptides, polysaccharides and combinations thereof. Preferred oligo [meth-] acrylamide derivative side chains include N-alkyl substituted [meth-] acrylalmide derivatives, linear random copolymer of [meth-]acrylamide derivative and hydrophylic comonomer, and combinations thereof. Techniques of grafting of oligo-N-isopropyl[meth]acrylamide side chains on a nonbiodegradable pH-sensitive homopolymer are described (Chen and Hoffman). The technique(s) of Chen and Hoffman were used herein to graft the oligo-N-isopropyl[meth-]acrylamide side chains on an alternative biodegradable polymers such as polyaminoacids, poly(phosphasenes), poly(caprolactone), polypeptides, polysaccharides and combinations thereof. The first step of the synthesis is either the free radical homopolymerization or the random copolymerization of the oligo-N-isopropyl[meth-]acrylamide side chains by free radical polymerization using an amino-terminated chain transfer agent, for example 2-aminoethanethiol hydrochloride. The next step is the coupling of the amino-terminated macromer to the carboxyl moieties of the biodegradable polymer using the activation reagent, e.g., dicyclohexyl carbodiimide. Other biodegradable polymers such as poly(phosphazenes) poly(caprolactone), polypeptides, polysaccharides and combinations thereof may also be grafted with the oligo-N-isopropyl[meth-]acrylamide side chains using similar synthetic techniques. The reaction solvent is non-aqueous, preferably a hydrocarbon, for example chloroform, dichloromethane, N,N-dimethylformamide or combinations thereof.

The resorbable and/or non-resorbable thermally reversible gel(s) of the present invention is/are useful as a therapeutic agent carrier. Therapeutic agent is a biologically active agent including but not limited to anti-cancer agents, hormones, antibiotics, narcotic antagonists, analgesics, anti-inflammatory agents, anti-depressant, anti-epileptic, anti-malarial agents, immunoactivators, growth factors, gene therapy agents, oligonucleotides, therapeutic peptides and proteins, and combinations thereof. More specifically, it is useful as a chemo-embolic material by combining the reversible copolymer with a chemo-therapeutic agent (CTA). At body temperature the reversible copolymer-CTA combination forms a reversible gel matrix containing the entrapped CTA, whereas at room temperature the reversible copolymer-CTA combination is a free-flowing (injectable) solution. The advantages of reversible gels as chemo-embolizing agents include: fast and effective embolization due to the immediate gel formation at body temperature, and easy incorporation of drugs either by simple mixing with copolymer solution wherein the drug or therapeutic agent is not covalently bonded to the reversible copolymer or by covalently bonding the drug or therapeutic agent to the reversible copolymer. The localized and controlled release of the CTA entrapped within the gel matrix enhances the efficacy and decreases the systemic toxic effects of chemotherapy.

Example 1

An experiment was conducted to demonstrate synthesis and thermoreversible gel formation of poly(N-isopropylacrylamide-co-acrylic acid)(NiPAAm/AAc). The

linear high molecular weight NiPAAm/AAc copolymers containing different amounts of AAc were synthesized by a free radical copolymerization.

The [meth-]acrylamide derivative was N-isopropylacrylamide (NiPAAm) (Fisher, Co.) that was recrystallized from hexane before use. The initiator 2,2'-azobis-isobutyronitrile (AIBN) (Eastman Kodak, Co.) was recrystallized from methanol. The hydrophilic comonomer was acrylic acid (AAc) (Aldrich Co.) that was purified before use by vacuum distillation at 39°C/10 mmHg. The reaction solvent, dioxane, HPLC grade (Aldrich Co.) was used as received. The mixture of [meth-]acrylamide derivative, initiator, hydrophilic comonomer, and solvent formed the reaction mixture.

The molar feed ratio of NiPAAm to AAc was varied as 99:1, 98:2 and 97:3. The copolymerization was carried out in dioxane (80 wt%), with the amount of AIBN initiator of 1.219×10^{-3} mols/L. The reaction proceeded at 60 °C for 18 hours. The resulting copolymer solution was diluted with fresh dioxane and added dropwise to a ten-fold excess of diethyl ether producing copolymer precipitation. The precipitated copolymer was isolated by filtration and drying. The isolated copolymer was redissolved in acetone and reprecipitated into ten-fold excess diethyl ether. The final, essential step of purification involved dialysis of aqueous copolymer solution through 12,000-14,000 molecular weight cut off (MWCO) dialysis membrane. Dialysis removed the residual unreacted monomer and all copolymer fractions with molecular weights smaller than the MWCO of the dialysis membrane, resulting in a purified copolymer product. The purified copolymer product was further freeze dried.

The removal of molecular weights below 12,000 from the synthesized copolymers was confirmed by gel permeation chromatography. The removal of unreacted monomers was confirmed by nuclear magnetic resonance.

The lower critical solution temperature (LCST) of the synthesized copolymers was evaluated by the cloud point determination method. In this method, 1 wt.% solutions of synthesized copolymers in phosphate buffered saline were heated from 20 to 50°C in 2-deg increments every 10 min. and the absorbance at 450 nm was measured. The cloud point, corresponding to the LCST was determined as the temperature at the inflection point in the absorbance versus temperature curve. NiPAAm homopolymer exhibited an LCST at 32°C. Copolymerization with hydrophilic comonomers shifted the LCST to the physiological temperature range of 36-38 °C. NiPAAm/AAc copolymer containing 2 mol% of AAc exhibited the LCST at 37°C.

Thermally reversible gel formation was studied at 37°C. The freeze-dried copolymer was dissolved in phosphate buffered saline (PBS) at different copolymer concentrations (0.5, 1.0, 1.5, 2.0, 2.5, and 5.0 wt%) forming copolymer solutions. The PBS was specifically 0.15M NaCl, 0.01M phosphates KH_2PO_4, and Na_2HPO_4. The copolymer solutions were thermally equilibrated at 37°C for 24 hours. The syneresis (amount of water expelled from the gel) was measured gravimetrically. Syneresis of thermoreversible hydrogels of N-isopropylacrylamide (NiPAAm) and its copolymers with acrylic acid (AAc) was affected by copolymer composition (0, 1, 2 mol% of AAc) and polymer concentration as shown in **FIG. 2**. In **FIG. 2** the amount of water retained in the gel is

plotted as a function of the initial copolymer concentration in solution (before geling). It was unexpectedly discovered that the solution containing at least about 2 wt% of the NiPAAm/AAc copolymer having at least about 2.0 mol % of AAc was able to produce a reversible gel exhibiting substantially no syneresis.

Example 2

An experiment was conducted to confirm the necessity of the minimum geling molecular weight cutoff. A geling polymer solution was made as in Example 1, but the solution was not dialyzed so that no low molecular weight species were removed. The result was a solution, milky in appearance, that did not form a gel.

Example 3

An experiment (release study) was conducted to demonstrate that the reversible gel would release a therapeutic agent at a controlled rate.

The release study was conducted using NiPAAm/AAc-2 copolymer containing 2 mol% of acrylic acid. Suspensions containing 20 and 33.3 wt% of 5-fluorouracil (5FU) in 5 wt.% copolymer solutions in PBS were prepared at room temperature by mixing and brief sonication. In all suspensions, the 5FU was physically mixed in the suspensions but was not covalently bonded to the copolymer. A 1 ml amount of copolymer/drug suspension was injected into a small dialysis tubing, (d=25 mm and MWCO 12,000-14,000). During the injection, the dialysis tubing was immersed in PBS equilibrated at 37°C. Instantaneous gel formation was observed inside the dialysis tubing. The tubing was then

sealed and a gentle mixing of the outside solution was turned on. Samples of the outside solution were taken at predetermined time intervals and replaced with the same amount of fresh PBS buffer. Concentration of 5FU was analyzed by UV spectrometry at 266 nm. The release profiles of 5FU from NiPAAm/AAc-2 copolymer are shown in **FIG. 3**, where fraction of the released drug is plotted as a function of time.

The release from gels containing 20 and 33 wt.% of drug were investigated. The release profiles differed markedly in terms of the observed initial burst effect. Within the firs 24 hr., the gel containing 20 wt.% of 5FU released almost 40% of drug, whereas the gel containing 33 wt.% of 5FU released less than 15% of drug. Usually, in the case of drug release from a highly hydrated copolymer matrix the initial release rate is greater for the gels with higher drug loading. To explain this apparent contradiction with the expected results we have to consider the substantial syneresis exhibited by the gel containing 20 wt.% of drug. In this case, the initial burst effect, normally caused by a fast diffusion from the outer gel layer, was enhanced by the amount of drug expelled from the gel matrix due to the syneresis. After 24 hr., i.e., after the initial burst effect, a constant release rate was observed for 120 hr for both gels, with a higher release rate observed for the gel containing 20 wt.% loading of 5FU.

Example 4

A further experiment was conducted to demonstrate the behavior of the gel during tissue perfusion in lymph nodes. A freeze dried copolymer of N-isopropylacrylamide with

acrylic acid (2 mol%) NiPAAm/AAc)] was dissolved in PBS as in Example 1. A dye Naphthol blue-black, electrophoresis reagent, from Sigma was added to the copolymer solution. In all solutions, the dye was physically mixed by dissolving into the solutions, but was not covalently bonded to the copolymer.

Canine lymph nodes were freshly isolated and equilibrated at 37 °C PBS for 30 min.

A 5wt% solution of NiPAAm/AAc in PBS, containing also a small amount (>0.01%) of the blue dye was prepared and cooled in an ice bath. Small aliquouts (0.2-0.3 ml) of the cold polymer solution were injected into the freshly isolated canine lymph nodes. After the injection, lymph nodes were kept at 37°C PBS for 10-15 min permitting the thermal gelation of the injected copolymer solution. The injected lymph nodes were then cut open with a razor blade to evaluate the extent of tissue perfusion. As shown in **FIG. 4a**, the dye perfusion within the lymph node **400** was limited to the extent of perfusion of the geled copolymer solution **402**, and was clearly visible.

As a control, dye solution in PBS only was injected into another lymph node **404** without mixing the dye into the geling solution. Dye **406** was not contained locally within the lymph node but diffused throughout and beyond the lymph node as illustrated in **FIG. 4b**. Injection of the dye solution alone resulted in no dye localization within the lymph node **404**.

Example 5

The polymerization was conducted as described in the Example 1 but using a different molar feed ratio of comonomers. The molar feed ratio of NiPAAm to AAc was varied as 98.4:1.6, 98.2:1.8, 98.1:1.9 and 98.0:2.0. Gelation temperature was measured for 5 wt % copolymer solutions in PBS, as described in Example 1. Gelation temperatures are listed in Table E5-1.

Table E5-1 Gelation temperature as a function of molar feed ratio

Molar feed ratio NiPAAm:AAc	Gelation temperature [°C]
98.4:1.6	34.0±0.1
98.2:1.8	35.5±0.1
98.1:1.9	36.5±0.1
98.0:2.0	37.4±0.1

CLOSURE

While a preferred embodiment of the present invention has been shown and described, it will be apparent to those skilled in the art that many changes and modifications may be made without departing from the invention in its broader aspects. The appended claims are therefore intended to cover all such changes and modifications as fall within the true spirit and scope of the invention.

CLAIMS

We claim:

1. A therapeutic agent carrier, comprising:

(a) a reversible geling copolymer, having a linear random copolymer of:

(i) an N-alkyl substituted [meth-]acrylamide derivitive; and

(ii) a hydrophilic comonomer, wherein an amount of said hydrophilic comonomer in the linear random copolymer is less than about 10 mole% wherein gelation occurs with substantially no synerisis,

said linear random copolymer in the form of a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff, and excluding a substantial amount of copolymer chains or polymer chains having molecular weights less than the minimum geling molecular weight cutoff;

(b) an aqueous solvent mixed with said reversible geling copolymer as a reversible geling solution; and

(c) a therapeutic agent mixed with said reversible geling solution as said therapeutic agent carrier.

2. The therapeutic agent carrier as recited in claim 1, wherein said amount is from about 1.6 mole% to about 2 mole%.

3. The therapeutic agent carrier as recited in claim 1, wherein said N-alkyl substituted [meth-]acrylamide is

selected from the group consisting of N-isopropyl[meth-]acrylamide, N,N-diethyl[meth-]acrylamide, N-[meth-]acryloylpyrrolidine, N-ethyl[meth-]acrylamide, and combinations thereof.

4. The therapeutic agent carrier as recited in claim 1, wherein said hydrophilic comonomer is hydrophilic [meth-]acryl- compound.

5. The therapeutic agent carrier as recited in claim 4, wherein said hydrophilic [meth-]acryl- compound is selected from the group consisting of carboxylic acid, [meth-]acrylamide, hydrophilic [meth-]acrylic acid ester, hydrophilic [meth-]acrylamide derivatives and combinations thereof.

6. The therapeutic agent carrier as recited in claim 5, wherein said carboxylic acid is selected from the group consisting of acrylic acid, methacrylic acid and combinations thereof.

7 The therapeutic agent carrier as recited in claim 6, wherein said hydrophilic [meth-]acrylamide derivatives are selected from the group consisting of N,N-diethyl[meth-]acrylamide, 2-[N,N-dimethylamino]ethyl[meth-]acrylamide, 2-[N,N-diethylamino]ethyl[meth-]acrylamide, or combinations thereof.

8. The therapeutic agent carrier as recited in claim 5, wherein said hydrophilic [meth-]acrylic ester is selected from the group consisting of 2-[N,N-diethylamino]ethyl[meth-

]acrylate, 2-[N,N-dimethylamino]ethyl[meth-]acrylate, and combinations thereof.

9. The therapeutic agent carrier as recited in claim 1, wherein said aqueous solvent is selected from the group consisting of water, and aqueous salt solution.

10. The therapeutic agent carrier as recited in claim 9, wherein said salt solution is a phosphate buffered saline.

11. The therapeutic agent carrier as recited in claim 10, wherein an amount of said solvent is from about 70 wt% to about 99 wt%.

12. The therapeutic agent carrier as recited in claim 1, wherein said therapeutic agent is selected from the group consising of anti-cancer agents, hormones, antibiotics, narcotic antagonists, analgesics, anti-inflammatory agents, anti-depressant, anti-epileptic, anti-malarial agents, immunoactivators, growth factors, gene therapy agents, oligonucleotides, therapeutic peptides and proteins, chemo-embolic material and combinations thereof.

13. A method of making a therapeutic agent carrier, comprising the steps of:

(a) mixing an N-alkyl substituted [meth-]acrylamide derivitive with a hydrophilic comonomer in a reaction solvent with an initiator forming a reaction mixture, wherein an amount of said hydrophilic comonomer in the linear random copolymer is less than about 10 mole%

wherein gelation occurs with substantially no synerisis;

(b) copolymerizing the reaction mixture and forming a first linear random copolymer having a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff, and excluding a substantial amount of copolymer chains or polymer chains having molecular weights less than the minimum geling molecular weight cutoff;

(c) isolating and purifying the copolymerized first linear random copolymer and obtaining a second linear random copolymer

(d) mixing the thermally reversible copolymer with an aqueous solvent and making a reversible geling solution; and

(e) adding a therapeutic agent and obtaining said therapeutic agent carrier.

14. The method as recited in claim 13 wherein said initiator is a free radical initiator.

15. The method as recited in claim 13, wherein said amount is from about 1.6 mole% to about 2 mole%.

16. The method as recited in claim 13, wherein said N-alkyl substituted [meth-]acrylamide is selected from the group consisting of N-isopropyl[meth-]acrylamide, N,N-diethyl[meth-]acrylamide, N-[meth-]acryloylpyrrolidine, N-ethyl[meth-]acrylamide, and combinations thereof.

17. The method as recited in claim 13, wherein said hydrophilic comonomer is hydrophilic [meth-]acryl- compound.

18. The method as recited in claim 17, wherein said hydrophilic [meth-]acryl- compound is selected from the group consisting of carboxylic acid, [meth-]acrylamide, hydrophilic [meth-]acrylic acid ester, hydrophilic [meth-]acrylamide derivatives and combinations thereof.

19. The method as recited in claim 18, wherein said carboxylic acid is selected from the group consisting of acrylic acid, methacrylic acid and combinations thereof.

20. The method as recited in claim 18, wherein said hydrophilic [meth-]acrylamide derivatives are selected from the group consisting of N,N-diethyl[meth-]acrylamide, 2-[N,N-dimethylamino]ethyl[meth-]acrylamide, 2-[N,N-diethylamino]ethyl[meth-]acrylamide, or combinations thereof.

21. The method as recited in claim 18, wherein said hydrophilic [meth-]acrylic ester is selected from the group consisting of 2-[N,N-diethylamino]ethyl[meth-]acrylate, 2-[N,N-dimethylamino]ethyl[meth-]acrylate, and combinations thereof.

22. The method as recited in claim 13, wherein said reaction solvent is selected from the group consisting of aqueous solvent, hydrocarbon solvent, and combinations thereof.

23. The method as recited in claim 22, wherein said aqueous solvent is selected from the group consisting of

water, aqueous salt solution and combinations thereof.

24. The method as recited in claim 22, wherein said hydrocarbon solvent is selected from the group consisting of oxygenated hydrocarbon, chlorinated hydrocarbon, aromatic hydrocarbon, and combinations thereof.

25. The method as recited in claim 24, wherein said oxygenated hydrocarbon is dioxane.

26. The method as recited in claim 24, wherein said chlorinated hydrocarbon is chloroform.

27. The method as recited in claim 24, wherein said aromatic hydrocarbon is benzene.

28. The method as recited in claim 13, wherein said aqueous solvent is selected from the group consisting of water, and aqueous salt solution.

29. The method as recited in claim 28, wherein said salt solution is a phosphate buffered saline.

30. The method as recited in claim 13, wherein said therapeutic agent carrier is selected from the group consising of is selected from the group consising of anti-cancer agents, hormones, antibiotics, narcotic antagonists, analgesics, anti-inflammatory agents, anti-depressant, anti-epileptic, anti-malarial agents, immunoactivators, growth factors, gene therapy agents, oligonucleotides, therapeutic

peptides and proteins, chemo-embolic material and combinations thereof.

31. A biodegradable thermally reversible graft copolymer, comprising:

(a) a biodegradable polymer; grafted with

(b) a side chain selected from the group consisting of homo-oligomers of [meth-]acrylamide derivatives, co-oligomers of [meth-]acrylamide derivatives, homo-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers, co-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers.

32. The copolymer as recited in claim 31, wherein said biodegradable copolymer is selected from the group consisting of polyaminoacids, poly(phosphasenes), poly(caprolactone), polypeptides, polysaccharides and combinations thereof.

33. The copolymer as recited in claim 31, wherein said oligo [meth-]acrylamide derivative is an N-alkyl substituted [meth-] acrylamide derivative.

34. The copolymer as recited in claim 31, wherein said oligo [meth-]acrylamide derivative side chain is randomly copolymerized with a hydrophilic comonomer as a linear random oligomer, said linear random oligomer having molecular weight less than a minimum geling molecular weight cutoff.

35. A reversible geling copolymer solution, comprising the copolymer as recited in claim 31, mixed with an aqueous solvent.

36. A therapeutic agent carrier, comprising:

the copolymer solution as recited in claim 35, mixed with a therapeutic agent.

37. A method of making a biodegradable thermally reversible copolymer, comprising the steps of:

(a) polymerizing a plurality of side chains selected from the group consisting of homo-oligomers of [meth-]acrylamide derivatives, co-oligomers of [meth-]acrylamide derivatives, homo-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers, co-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers, said side chain having a first active group; and

(b) coupling the side chains to a biodegradable polymer having a plurality of second active groups wherein said first active group connects to one of the plurality of the second active groups.

38. The method as recited in claim 37, wherein said biodegradable polymer is selected from the group consisting of polyaminoacid, poly(phosphazenes), poly(caprolactone), polypeptides, polysaccharides and combinations thereof.

39. The method as recited in claim 37, wherein said polymerizing is a free radical copolymerization wherein the first active group is an amino which originates from an amino-terminated chain transfer agent.

40. The method as recited in claim 39, wherein said amino-terminated chain transfer agent is 2-aminoethanethiol hydrochloride.

41. The method as recited in claim 37, wherein said coupling is with an activation reagent.

42. The method as recited in claim 39, wherein said activation reagent is dicyclohexyl carbodiimide.

43. The method as recited in claim 37, wherein said oligo [meth-]acrylamide derivative is an N-alkyl substituted [meth-] acrylamide derivative.

44. The method as recited in claim 37, wherein said oligo [meth-]acrylamide derivative side chain is randomly copolymerized with a hydrophilic comonomer as a linear random oligomer, said linear random oligomer having molecular weight less than a minimum geling molecular weight cutoff.

45. The method as recited in claim 37, further comprising the step of:

mixing the biodegradable copolymer with an aqueous solvent.

46. The method as recited in claim 45, further comprising the step of:

adding a therapeutic agent and obtaining a therapeutic agent carrier.

ABSTRACT OF THE DISCLOSURE

The present invention is a thereapeutic agent carrier having a thermally reversible gel or geling copolymer that is a linear random copolymer of an [meth-]acrylamide derivative and a hydrophilic comonomer, wherein the linear random copolymer is in the form of a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum geling molecular weight cutoff and a therapeutic agent.

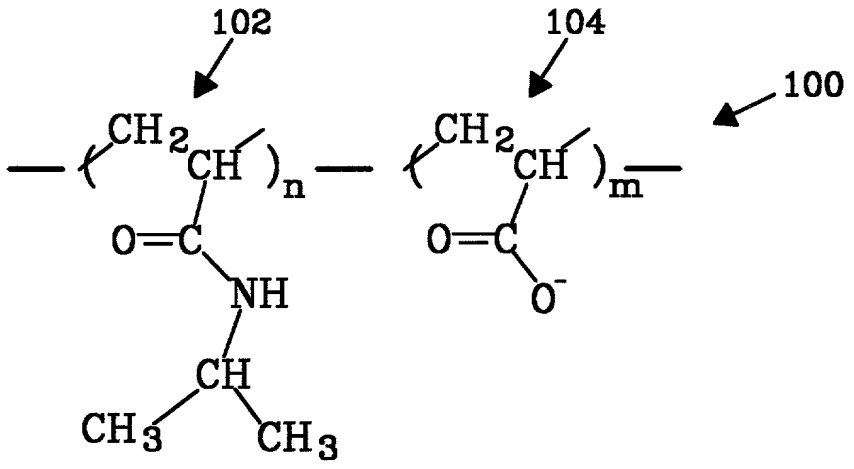
102
104
100
CH2
CH
n
m
O=C
NH
O-
CH
CH3
CH3

Fig. 1

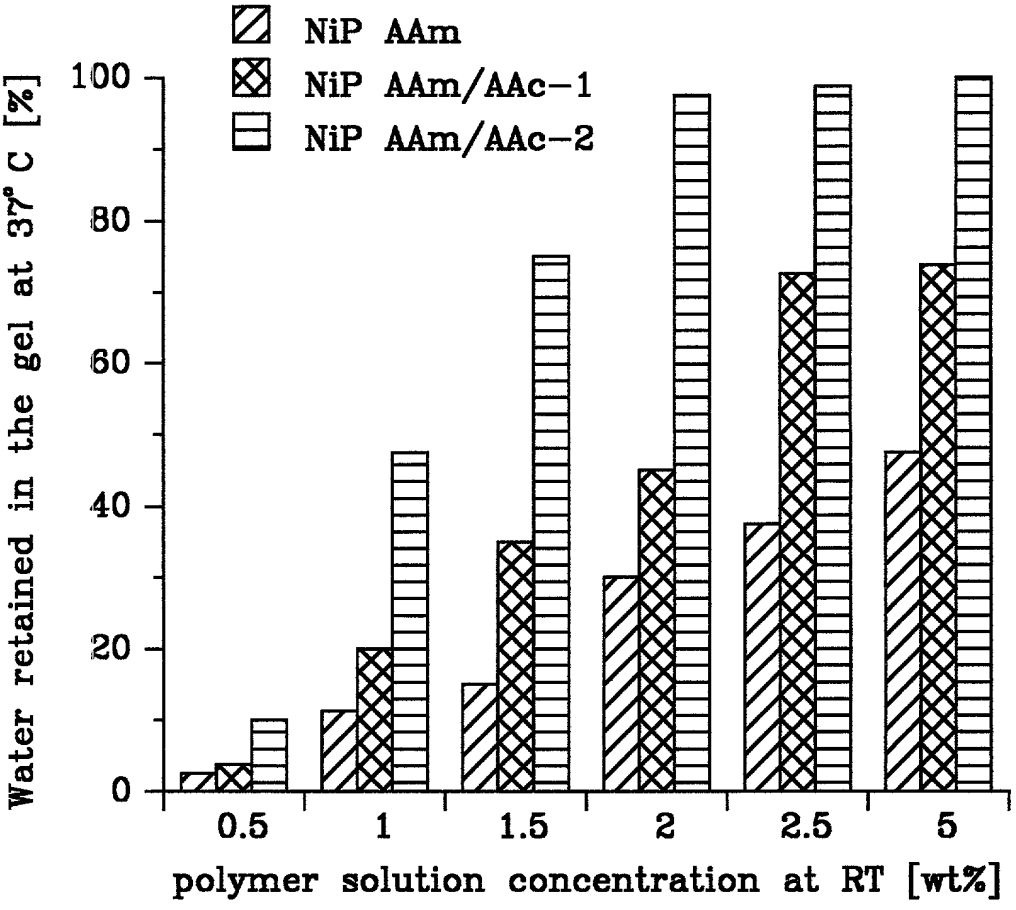
NiP AAm
NiP AAm/AAc-1
NiP AAm/AAc-2
Water retained in the gel at 37° C [%]
100
80
60
40
20
0
0.5
1
1.5
2
2.5
5
polymer solution concentration at RT [wt%]

Fig. 2

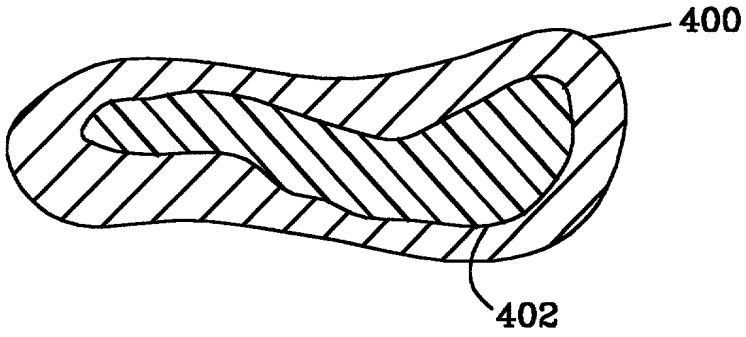

Fig. 4a

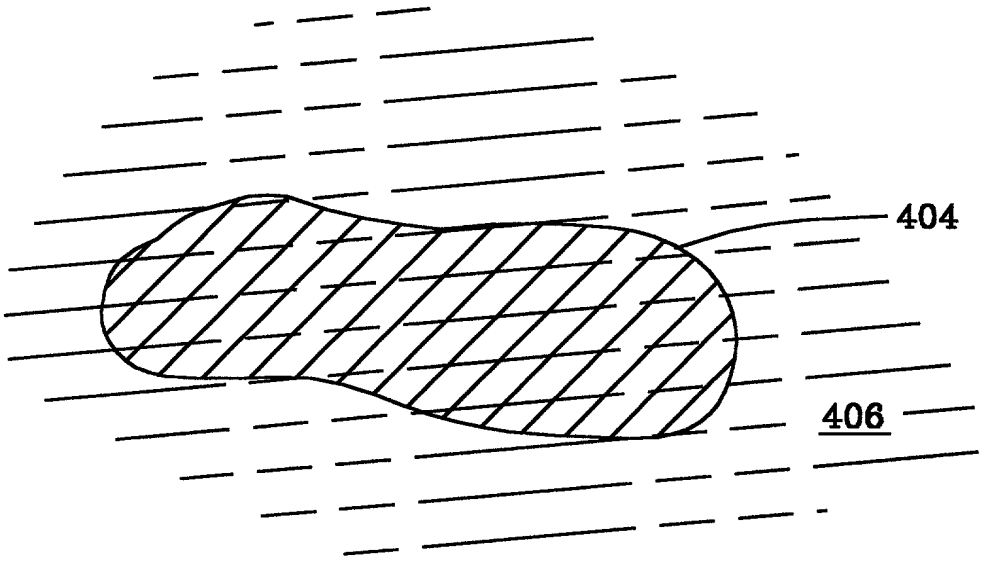

Fig. 4b

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PATENT

File No. E-1537 CIP

COMBINED DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name,

I believe I am the original, first, and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled REVERSIBLE GELING CO-POLYMER AND METHOD OF MAKING, the specification of which

[X] is attached hereto.

[ ] was filed on _____ as
Application Serial No. _____

[ ] and was amended on _____
(if applicable)

[ ] with amendments through _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

[X] no such applications have been filed

[ ] such applications have been filed as follows

Prior Foreign Application(s)			Priority Claimed	
	NONE			
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No
(Number)	(Country)	(Day/Month/Year Filed)	[ ] Yes	[ ] No

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

	NONE	
08/870,368	6/6/97	Pending
(Application Serial No.)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application, to file a corresponding international application, and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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